Lung Transplantation for Pulmonary Sarcoidosis. 25 Years of Experience in the United States

Supplement Material

Methods

Data and design

This study used data from the Standard Transplant Analysis and Research (STAR) files collected by the Organ Procurement and Transplantation Network (OPTN). The STAR files report a longitudinal de-identified patient database including data on all organ donor and transplant recipients in the United States (US). The Health Resources and Services Administration of the US Department of Health and Human Services provides oversight of the activities of the OPTN. The present work was exempt from the University of Minnesota School of Medicine Institutional Review Board.

We performed a retrospective analysis of all patients undergoing lung transplantation between October 1, 1987 and December 31, 2012. Our inclusion criteria included all lung-only first-time transplants. Exclusion criteria included multiple organ transplantation. We identified patients diagnosed with sarcoidosis, and compared that group to all other transplanted cases. The control group included patients diagnosed with idiopathic pulmonary fibrosis, cystic fibrosis, chronic obstructive pulmonary disease, primary pulmonary arterial hypertension, and “other” diagnoses.

Outcomes and definitions

The primary outcome was median survival rate. The secondary outcomes were allograft dysfunction rates, namely; the incidence of bronchiolitis obliterans syndrome (BOS), re-

transplantation, or new requirement for supplemental oxygen (O2) at rest post-transplant. Data for recipient survival rates were censored at 10 years.

Statistical analysis

Continuous data were reported as mean ± standard deviation, and compared using t-test. Categorical variables were compared using chi-square (χ^2) test. The method of Kaplan Meier (KM) with log-rank testing was used to assess and compare unadjusted survival rates between sarcoidosis and control groups, in a time to death fashion. Cox proportional hazards regression analysis was used to determine the variables predictive of mortality. The outcome of interest was all-cause mortality. All other outcomes, including re-transplantation, alive or lost to follow up were censored in the model. Variables that were associated with death (vs survivors) with $p < 0.05$ in univariate analysis were eligible to be included in the multivariate model. The covariates examined include sarcoidosis, recipient sex, age, race, need for mechanical ventilation, double-lung transplantation, graft ischemic time, lung allocation score (LAS) era, and donor age, sex and race on survival in lung transplantation. Results were reported as hazard ratio (HR) with 95% confidence interval (95% CI). The Levene and Kolmogorov–Smirnov tests were used to assess for the distribution of data across the subgroups, and the proportional hazard assumptions over time were met. All data variables in the registry that reported values for less than 2/3 of the entire patient cohort were excluded from the study; these included pre-transplant hemodynamics, post-transplant forced vital capacity, forced expiratory volume, and pre-transplant oxygen requirements. All tests were two-tailed, and a p-value <0.05 was considered statistically significant. Analyses were performed using SAS version 9.0 (SAS Institute, Cary NC).

Limitations

Our study had several limitations. The retrospective nature of our study required us to assume integrity of data received from the referring transplant centers. Therefore, we were constrained by the type and form of data collected. However, given the rarity and low number of sarcoid transplants, utilization of registry data allowed for more robust analysis and facilitated hypothesis formulation. Since patient management in terms of post-transplant care is center-dependent, we cannot discount that center-specific factors may had affected our findings. Finally, we did not have any sufficient data about disease recurrence post-transplant, pulmonary function testing and the specific immunosuppressive regimens used. The universal definition of BOS, as a chronic decline in FEV1 due to the development of BOS post-transplant, represented the major criteria of diagnosis since the 1980s. However, as a consequence of new insights into the pathophysiology of BOS and the evolution of treatment strategies, the first statement on BOS diagnostic criteria was published in 1993[1], updated in 2002[2], with a likely new term use (chronic lung allograft dysfunction) in the near future[3]. Thus, we were constrained by the varying definitions used by the OPTN since 1987.

Table 1S. Multivariate predictors of all-cause mortality, in the total cohort and the sarcoid cohort.

	Total cohort		**Sarcoid cohort**	
Variable	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Sarcoidosis	0.96(0.85-1.08)	0.51	--	--
Age	1.003(1.002-1.005)	<0.001	1.00(0.99-1.01)	0.90
Male	1.03(0.99-1.08)	0.17	0.90(0.69-1.18)	0.45
Caucasian	0.95(0.89-1.02)	0.14	0.84(0.65-1.10)	0.21
Mechanical ventilation	1.42(1.19-1.70)	<0.001	0.99(0.24-4.03)	0.98
Double lung transplant	0.80(0.76-0.84)	<0.001	0.76(0.58-0.99)	0.04
Graft ischemic time	0.99(0.98-1.00)	0.06	1.06(0.99-1.13)	0.11
Donor-Caucasian	0.88(0.85-0.92)	<0.001	1.00(0.79-1.28)	0.99
Donor-male	1.00(0.96-1.05)	0.87	1.31(1.00-1.72)	0.05
Donor-age	1.003(1.001-1.004)	0.001	1.01(1.00-1.01)	0.21
LAS era	0.90(0.86-0.95)	<0.001	0.74(0.56-0.97)	0.03

LAS: lung allocation score.

Table 2S. Single versus double lung transplantation in the sarcoid cohort

Variable	Sarcoid (n=695)	Single-lung (n=216, 31.1%)	Double-lung (n=479, 68.9%)	p-value
Pre-transplant				
Age, year	49.9±8.7	50±8.9	49.8±8.6	0.58
Males, n(%)	300(43.0)	81(37.5)	217(45.3)	0.05
Caucasian, n(%)	227(32.6)	91(42.1)	135(28.2)	<0.001
Waiting time, month	5.9(0-97)	7.5(0-60)	5.1(0-97)	0.18
Transplant				
Life support, n(%)				
Inhaled NO	0(0)	0(0)	0(0)	1.0
Prostacyclin	4(0.5)	4(0.8)	0(0)	0.24
ECMO-bridge	0(0)	0(0)	0(0)	1.0
Mechanical ventilation	5(0.7)	5(1.0)	0(0)	0.13
Graft ischemic time, hour	5.1±1.8	4.1±1.5	5.6±1.8	<0.001
Post-LAS, n(%)	380(54.7)	66(30.6)	314(65.6)	<0.001
Donor				
Age, year	33.7±13.7	32.5±13.2	34.2±13.9	0.12
Male, n(%)	369(52.9)	127(58.8)	241(50.3)	0.04
Caucasian, n(%)	432(62)	144(66.7)	287(59.9)	0.09
Post-transplant				
Survival				
Median (IQR), month	69.7(60.2-79.3)	61.5(41.8-81.1)	82.2(64.5-100.0)	0.01
1-year (%)	71	67	72	
5-year (%)	50	43	54	
10-year (%)	28	23	32	
Allograft dysfunction				
Re-transplanted, n(%)	15(2.2)	6(2.8)	9(1.9)	0.46
BOS, n(%)	222(31.9)	83(38.4)	139(29.0)	0.01
New O_2 requirement, n(%)	129(27.5)	63(39.9)	66(21.2)	<0.001

BOS: post-transplant bronchioalveolitis syndrome. IQR: interquartile range. NO: inhaled nitric oxide, ECMO: extracorporeal membrane oxygenation. Prostacyclin in the intravenous or inhaled formulations.

Figure 1S. Unadjusted Kaplan-Meier survival curve comparing double lung transplant group to single lung transplant group in the sarcoid cohort.

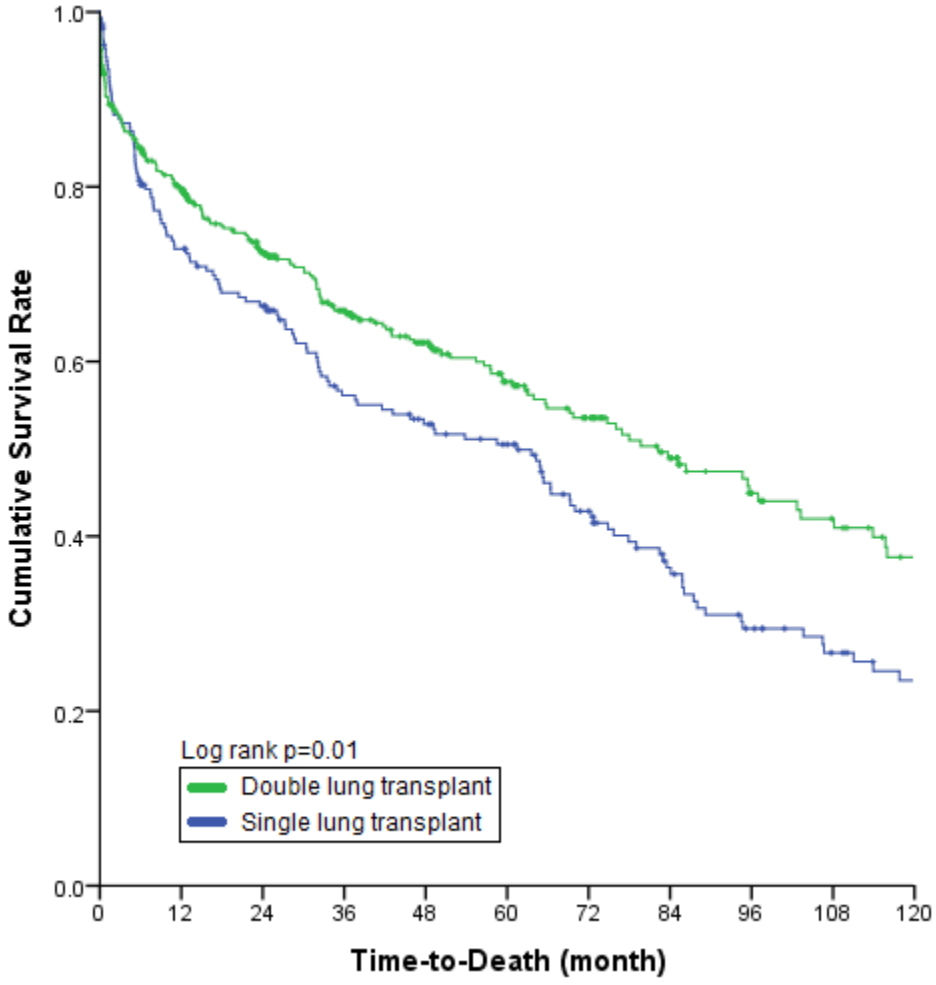
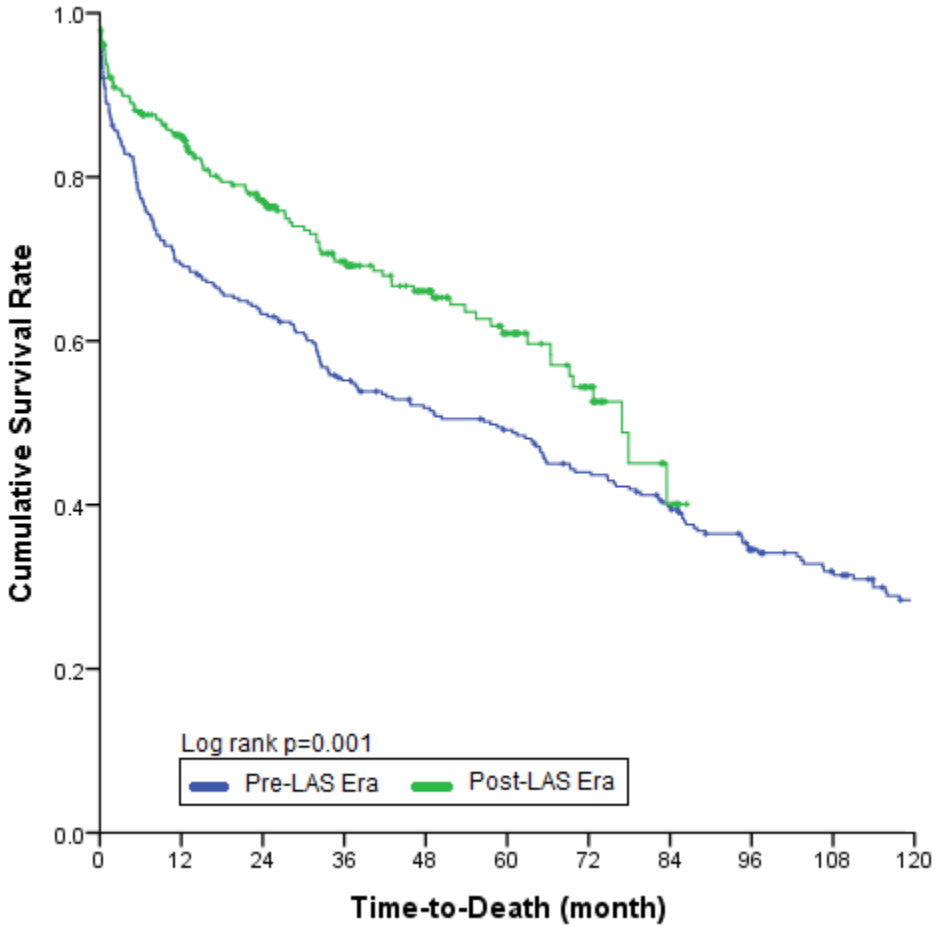


Table 3S. Lung allocation score in the sarcoid cohort

Variable	Sarcoid (n=695)	Pre-LAS (n=315, 45.3%)	Post-LAS (n=380, 54.7%)	p-value
Pre-transplant				
Age, year	49.9±8.7	47.8±8.7	51.7±8.2	<0.001
Males, n(%)	300(43.0)	112(35.6)	186(48.9)	<0.001
Caucasian, n(%)	227(32.6)	108(34.3)	118(31.1)	0.37
Waiting time, month	5.9(0-97)	9.3(0-65)	3.75(0-97)	<0.001
Transplant				
Life support, n(%)				
Inhaled NO	0(0)	0(0)	0(0)	1.0
Prostacyclin	4(0.5)	0(0)	4(1.1)	0.11
ECMO-bridge	0(0)	0(0)	0(0)	1.0
Mechanical ventilation	5(0.7)	1(0.3)	4(1.1)	0.25
Graft ischemic time, hour	5.1±1.8	4.8±1.8	5.4±1.8	<0.001
Double lung transplant, n(%)	480(68.9)	165(52.4)	314(82.6)	<0.001
Donor				
Age, year	33.7±13.7	32.5±13.7	34.7±13.7	0.04
Male, n(%)	369(52.9)	181(57.5)	187(49.2)	0.03
Caucasian, n(%)	432(62)	211(67.0)	220(57.9)	0.01
Post-transplant				
Survival				
Median (IQR), month	69.7(60.2-79.3)	57.5(39.7-75.4)	76.9(67.2-86.6)	0.001
1-year (%)	71	63	77	
5-year (%)	50	44	56	
10-year (%)	28	13	--	
Allograft dysfunction				
Re-transplanted, n(%)	15(2.2)	9(2.9)	6(1.6)	0.26
BOS, n(%)	222(31.9)	123(39.0)	99(26.1)	<0.001
New O_2 requirement, n(%)	129(27.5)	70(31.8)	59(23.7)	0.049

BOS: post-transplant bronchioalveolitis syndrome. IQR: interquartile range. NO: inhaled nitric oxide. ECMO: extracorporeal membrane oxygenation. Prostacyclin in the intravenous or inhaled formulations.

Figure 2S. Unadjusted Kaplan Meier Curve comparing post-LAS sarcoid lung transplant group to pre-LAS sarcoid lung transplant group in the sarcoid cohort.



References

1. Cooper JD, Billingham M, Egan T, et al. A working formulation for the standardization of nomenclature and for clinical staging of chronic dysfunction in lung allografts. International Society for Heart and Lung Transplantation. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation.* Sep-Oct 1993;12(5):713-716.

2. Bankier AA, Van Muylem A, Knoop C, Estenne M, Gevenois PA. Bronchiolitis obliterans syndrome in heart-lung transplant recipients: diagnosis with expiratory CT. *Radiology.* Feb 2001;218(2):533-539.

3. Verleden GM, Raghu G, Meyer KC, Glanville AR, Corris P. A new classification system for chronic lung allograft dysfunction. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation.* Feb 2014;33(2):127-133.